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EXAMINER
HUYNH, PHUONG N

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/402,636	Applicant(s) MASCAX ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication app ars on the cov r sheet with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11,17,18,20-22 and 41-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,11,17,18,20-22 and 41-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-7, 9, 11, 17-18, 20-22, and 41-48 are pending.

2. In view of the amendment filed 8/14/02, the following rejections remain.

3. In response to Applicants' request for a telephonic interview, a telephone call was made to Teresa J. Welch and Gregory J Hartwig on Oct 29, 2002. However, the Examiner was not able to reach the undersign of record.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7, 9, 11, 17-18, 20-22 and 41-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses only a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest wherein the vitamin D moiety has a formula II as shown on page 11 lines 13-19 bridging page 12 lines 1 to 6 of the specification, wherein said moiety is selected from the group consisting of 1α previtamin D, 1α, 24-$(OH)_2$D2-aminoalkyl, 11α, 25-$(OH)_2$D2-aminoalkyl linked to the hydroxyl group at C-1, C-3, C-24 and C-25 of said vitamin D moiety and wherein the targeting moiety is bisphosphonate.

The specification does not reasonably provide a **written description** of (1) *any* conjugate comprising *any* "vitamin D moiety" associated with *any* target molecule moiety having an affinity for *any* tissue of interest, (2) *any* conjugate comprising *any* "vitamin D moiety" associated with *any* target molecule moiety having an affinity for *any* tissue of interest wherein the molar ratio of the at least one vitamin D moiety to the at least one target molecule moiety is 1:1; (3) *any* conjugate comprising *any* "vitamin D moiety" associated with *any* target molecule moiety having an affinity for *any* tissue of interest wherein the vitamin D moiety is associated

with the target molecule moiety via a connecting group such as a linkage group formed by modification of vitamin D moiety and the target moiety to form a bond therebetween, a bifunctional connector, and the connecting group and at least one additional connecting group (4) *any* conjugate comprising *any* "vitamin D moiety" associated with *any* target molecule moiety having an affinity for *any* tissue of interest further comprising at least any one therapeutic agent other than a vitamin D moiety conjugated therewith such as estrogens or their equivalents, antiestrogen, calcitonin, bisphosphonates, calcium supplements, cobalamin, pertussis toxin, boron, dehydroepiandrosterone, transforming bone growth factor beta, activin, and bone morphogenic protein, (5) *any* pharmaceutical composition comprising *any* conjugate comprising *any* "vitamin D moiety" associated with *any* target molecule moiety having an affinity for *any* tissue of interest and a suitable pharmaceutically acceptable carrier, (6) *any* pharmaceutical composition mentioned above further comprising a differentially degradable coating encapsulating the conjugate for time release delivery of the conjugate such as enteric coating, (7) *any* conjugate comprising *any* "vitamin D moiety" associated with *any* target molecule moiety having an affinity for *any* tissue of interest with the proviso that the tissue is not plasma, (8) *any* conjugate comprising *any* "vitamin D moiety" associated with *any* target molecule moiety having an affinity for *any* tissue of interest wherein the conjugate includes such as the ones recited in claim 42, (9) *any* pharmaceutical composition comprising *any* conjugate comprising *any* "vitamin D moiety" associated with *any* target molecule moiety having an affinity for *any* tissue of interest and a suitable pharmaceutically acceptable carrier with the proviso that the tissue is not plasma, (10) *any* conjugate comprising at last *any* one vitamin D moiety associated with a target molecule having an affinity for *any* tissue of interest, the targeting molecule moiety including at least one of *any* polyaspartic acid, *any* polyglutamic acid, *any* aminophosphosugar, *any* protein with bone mineral binding domains, *any* steroid, *any* metal ion-amino acid chelate, *any* antibody and combination thereof for targeting to bone. There is insufficient written description about the **structure** associated with function of *any* "vitamin D moiety" and *any* "targeting molecule moiety", *any* steroid, *any* aminophosphosugar, *any* metal ion-amino acid chelate, *any* antibody and combination thereof.

The specification discloses only six conjugates having one specific targeting moiety such as bisphosphonate linked to the hydroxyl group at C-1, C-3, C-24 and C-25 of said vitamin D such as 1α, 24-$(OH)_2$D2-aminoalkyl, 11α, 25-$(OH)_2$D2-aminoalkyl. Given the lack of a written description of any additional conjugate comprising any vitamin D moiety associated with any

target molecule moiety such as any steroid, any antibody, any combination thereof, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The declaration under 37 C.F.R. 1.132 of Jeffrey W. Driscoll filed 9/24/01 and applicants' argument filed 8/14/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the description adequately supports the claims in such as way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. (2) In view of Jeffrey W. Driscoll's Declaration, Applicants should not be limited to the disclosed spies, as the scope of the claimed genus.

However, Claims 1, 20 and 44 are drawn to any conjugate comprising at least *any* one vitamin D moiety associated with *any* target molecule moiety having an affinity for *any* tissue of interest such as bone and prostate. There is insufficient written description about he structure associated with function of *any* "vitamin D moiety", and *any* "targeting molecule" such as the binding specificity of *any* antibody, *any* steroid, *any* metal ion-amino acid chelate, much less about targeting any conjugate to the tissue of interest such as bone or prostate for preventing *any* abnormal growth and hyperproliferation of *any* cells.

Further, the specification discloses only six conjugates having one specific targeting moiety such as bisphosphonate linked to the vitamin D moiety such as hydroxyl group at C-1, C-3, C-24 and C-25 of said vitamin D such as 1α, 24-$(OH)_2$D2-aminoalkyl, 11α, 25-$(OH)_2$D2-aminoalkyl for targeting vitamin D to the bone. The specification does not teach the specific antibody that target the conjugate to the bone, much less steroid other than DHEA, and estrogen for targeting vitamin D to the bone.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-5, 11 and 20 stand rejected under 35 U.S.C. 102(a) as being anticipated by Kobayashi *et al* (of record, Analytical Biochemistry 244: 374-383, Jan 1997; PTO 892).

Kobayashi *et al* teach a conjugate comprising at least one vitamin D moiety such as 1,25(OH)2D3 conjugated to a target molecule moiety such as BSA, which inherently has an affinity for plasma (See Fig 1, page 375 column 2, last paragraph, page 375 column 1, in particular). The reference vitamin D moiety and target molecule moiety are connected via a connecting group such as chemical bridge or bond at the C-11 α position (See Fig 1, in particular) or a connecting group such as N- hydroxy-succinimidyl ester which is a bifunctional connector to form a bond between said vitamin D and BSA (See page 375, third full paragraph, in particular). Claim 2 is included in this rejection because the vitamin D moiety is conjugated to the target molecule moiety, which is 1:1 ratio. Claim 11 is included in this rejection because N-hydroxy-succinimidyl ester is a good reagent for reaction with Lysine, which is an amino acid that forms an amide linkage through α-amino group or the ε aliphatic amino group. In addition, the N-hydroxy-succinimidyl ester reacts with the carboxyl group or thiol group of Cysteine amino acid residue that can be chelated. Claim 20 is included in this rejection because the reference teaches the reference conjugate in isotonic saline for injection, which is a suitable pharmaceutically acceptable carrier and adjuvant. The term "comprising" is open ended. It expands the claimed composition to include additional compound such as adjuvant, which reads on the reference composition. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 8/14/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 1 recites "a conjugate comprising at least one vitamin D moiety associated with a target molecule having an affinity for a tissue of interest". Applicants have claimed only those conjugates wherein a "targeting molecule" or "targeting molecules" as defined in the specification on page 9, lines 13-14 linked to a vitamin D moiety. (2) Although Kobayashi may disclose a "conjugate of 1,25(OH)2D3 with bovine serum albumin,

it does not teach or suggest that BSA is a "target molecule moiety" as defines in Applicants' specification. (3) Kobayashi et al does not teach a pharmaceutical comprising a pharmaceutically acceptable carrier as recited in claim 20.

In response to Applicants' argument that claim 1 recites "a conjugate comprising at least one vitamin D moiety associated with a target molecule having an affinity for a tissue of interest", a compound is compound irrespective of its affinity for tissue of interest. Further, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). See MPEP 2145.

In response to Applicants' argument that Kobayashi et al does not teach a pharmaceutical comprising a pharmaceutically acceptable carrier as recited in claim 20, Kobayashi *et al* teach conjugate in isotonic saline for injection, which is a suitable pharmaceutically acceptable carrier. The term "comprising" is open ended. It expands the claimed pharmaceutical composition to include additional compound such as Freund's adjuvant to read on the reference pharmaceutical composition.

8. Claims 1-4 stand rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 4,292,250 (Sept 1981, PTO 892).

The '250 patent teaches a conjugate comprising at least one vitamin D moiety such as 25 hydroxy vitamin D2 and its derivatives conjugated to a target molecule moiety such as glucuronide wherein the glucoronide is linked to said vitamin D moiety at a position on the vitamin D moiety which is C-25 at a 1:1 ratio via a connecting group that form a bond between them. The reference glucoronide inherently targets the vitamin D to the plasma. The '250 patent teaches the reference conjugate by virtual of its similarity to 25 hydroxy vitamin D2, which is a known biologically potent compound can be substitute for 25 hydroxy vitamin D2 in various therapeutic applications and particularly where the water solubility of the glucuronic acid compound is a necessity or advantage (See abstract, in particular). The reference conjugate offers additional advantages that it is water-soluble and hence lends it to intravenous and intramuscular dosage formulations and to administering to patients who have difficulty in assimilating lipids (See column 1, lines 65-68, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 8/14/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 1 recites "a conjugate comprising at least one vitamin D moiety is associated with a target molecule having an affinity for a tissue of interest". Applicants have claimed only those conjugates wherein a "targeting molecule" or "targeting molecules" as defined in the specification on page 9, lines 13-14 linked to a vitamin D moiety. (2) DeLuca (the '250 Patent) does not teach the subject matter of claim 1. The conjugate of DeLuca 25-hydroxy vitamin D2 25-glucuronide derivatives among which is 25-hydroxy vitamin D2 25-glucurronic acid where glucuronide is not a target molecule moiety.

In response to Applicants' argument that claim 1 recites "a conjugate comprising at least one vitamin D moiety associated with a target molecule having an affinity for a tissue of interest", a compound is compound and affinity for tissue of interest is an inherent property of the compound. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). See MPEP 2145.

In response to Applicants' argument that glucuronide is not a target molecule moiety, the reference glucuronide moiety inherently has the property of a molecule that influences the metabolism of the tissue interest (page 7 third paragraph of the response) such as the kidney and target to the plasma because the glucuronide moiety makes the reference conjugate more soluble.

In response to Applicants' argument that DeLuca et al (the '250 patent) does not teach a pharmaceutical comprising a pharmaceutically acceptable carrier as recited in claim 20, claim 20 is hereby withdrawn from this rejection and therefore the argument is moot.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 6, 17 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi *et al* (of record, Analytical Biochemistry 244: 374-383, Jan 1997; PTO 892) or US Pat No. 4,292,250 (Sept 1981, PTO 892) each in view of US Pat No. 5,576,309 (Nov 1996, PTO 892).

The teachings of Kobayashi *et al* and the '250 patent have been discussed supra.

The claimed invention as recited in claim 6 differs from the references only by the recitation that the vitamin D moiety is associated with the target molecule via the connecting group and at least one additional connective group.

The claimed invention as recited in claim 17 differs from the references only by the recitation that the conjugate further comprising at least one therapeutic agent other than a vitamin D moiety conjugated therewith.

The claimed invention as recited in claim 18 differs from the references only by the recitation that the conjugate wherein the therapeutic agent is a bone-therapeutic agent such as conjugated estrogens or their equivalents.

The '309 patent teaches various estradiol derivatives conjugated to a drug such as chlorambucil at the 3, 17 OH group (See Table 9-10, columns 22-23, column 5, lines 25,-44, in particular) and is useful for a pharmaceutical composition for treating tumor (See claims of '309, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate at least one therapeutic agent such as the estradiol derivative conjugates as taught by the '309 patent to the vitamin D conjugate linked through the C-11α position as taught by Kobayashi *et al* or the C-25 position as taught by the '250 patent. The recitation of one additional connective group is an obvious variation of the connective group as taught by Kobayashi *et al*. From the combined teachings of the references, it is apparent that one

of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '309 patent teaches \various types of estradiol derivative conjugates to a drug such as chlorambucil at the 3, 17 OH group (See Table 9-10, columns 22-23, column 5, lines 25-44, in particular) and is useful for a pharmaceutical composition for treating tumor (See claims of '309, in particular). The '250 patent teaches the reference conjugate by virtual of its similarity to 25 hydroxy vitamin D2, which is a known biologically potent compound, can be substitute for 25 hydroxy vitamin D2 in various therapeutic applications, particularly where the water solubility of the glucuronic acid compound is a necessity or advantage (See abstract, in particular). Kobayashi *et al* teach vitamin D moiety such as 1,25(OH)2D3 can be conjugated to any target molecule moiety via a connecting group such as chemical bridge or bond or a connecting group such as N-succinimidyl ester at the 11 α position (See Fig 1, page 375 column 2, last paragraph, page 375 column 1, in particular).

Applicants' arguments filed 8/14/02 have been fully considered but are not found persuasive.

Applicants' position is that claims 17-18 are depended on allowable claim 1 and is therefore allowable.

However, claim 1 is not allowable because of the reasons set forth above.

The claimed invention as recited in claim 6 differs from the references only by the recitation that the vitamin D moiety is associated with the target molecule via the connecting group and at least one additional connective group.

The claimed invention as recited in claim 17 differs from the references only by the recitation that the conjugate further comprising at least one therapeutic agent other than a vitamin D moiety conjugated therewith.

The claimed invention as recited in claim 18 differs from the references only by the recitation that the conjugate wherein the therapeutic agent is a bone-therapeutic agent such as conjugated estrogens or their equivalents.

The '309 patent teaches various types of estradiol derivative conjugates to a drug such as chlorambucil at the 3, 17 OH group (See Table 9-10, columns 22-23, column 5, lines 25, -44, in particular) and is useful for a pharmaceutical composition for treating tumor (See claims of '309, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate at least one therapeutic agent such as the estradiol derivative conjugates as taught by the '309 patent to the vitamin D conjugate linked through the C-11α position as taught by Kobayashi *et al* or the C-25 position as taught by the '250 patent. The recitation of one additional connective group is an obvious variation of the connective group as taught by Kobayashi *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '309 patent teaches 18 types of various estradiol derivatives conjugated to a drug such as chlorambucil at the 3, 17 OH group (See Table 9-10, columns 22-23, column 5, lines 25,-44, in particular) and is useful for a pharmaceutical composition for treating tumor (See claims of '309, in particular). The '250 patent teaches the reference conjugate by virtual of its similarity to 25 hydroxy vitamin D2, which is a known biologically potent compound can be substitute for 25 hydroxy vitamin D2 in various therapeutic applications, particularly where the water solubility of the glucuronic acid compound is a necessity or advantage (See abstract, in particular). Kobayashi *et al* teach vitamin D moiety such as 1,25(OH)2D3 can be conjugated to any target molecule moiety via a connecting group such as chemical bridge or bond or a connecting group such as N-succinimidyl ester at the 11 α position (See Fig 1, page 375 column 2, last paragraph, page 375 column 1, in particular).

12. Claims 21-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi *et al* (of record, Analytical Biochemistry 244: 374-383, Jan 1997; PTO 892) or US Pat No. 4,292,250 (Sept 1981, PTO 892) each in view of US Pat No. 6,309,666 (Oct 2001, PTO 892).

The teachings of Kobayashi *et al* and the '250 patent have been discussed supra.

The claimed invention as recited in claim 21 differs from the references only that the pharmaceutical composition further comprising a differentially degradable coating encapsulating the conjugate for time release delivery of the conjugate.

The claimed invention as recited in claim 22 differs from the references only that the pharmaceutical composition wherein said coating is an enteric coating.

The '666 patent teaches a pharmaceutical preparation in the form of a coated capsule such as enteric coating such as gelatin polymer capsule for time release delivery of any kind of

medicament such as prednisolone (See entire document, abstract, column 6 lines 66-67 bridging column 7, lines 1-7, column 20, lines 25, in particular). The '666 patent teaches the time period from the discharge of the pharmaceutical preparation from the stomach till the contents of the hard capsule start to be released can be controlled to any length by selecting the kind and/or amount of polymer(s) used for a low pH soluble polymer film and/or the kind of the acidic substance (See column 3, lines 31-38, in particular). The reference pharmaceutical preparation has the advantage that the contents of the hard capsule can be released quickly and at any desired site of the lower part of the digestive tract (See column 3, lines 39-42, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the prednisolone in the polymer capsule for time release delivery as taught by the '666 patent for the conjugate as taught by Kobayashi *et al* and the '250 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '666 patent teaches that the enteric coating pharmaceutical preparation has the advantage that the contents of the hard capsule can be released quickly and at any desired site of the lower part of the digestive tract (See column 3, lines 39-42, in particular).

Given the absence of rebuttal to the outstanding rejection of record in applicant's amendment, filed 8/14/02, this rejection is maintained for the reasons of record.

13. The following new grounds of rejection are necessitated by the amendment filed 8/14/02.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 44-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a conjugate comprising at least one vitamin D moiety associated with a target molecule having an affinity for bone wherein the vitamin D moiety has a formula II as shown on page 11 lines 13-19 bridging page 12 lines 1 to 6 of the specification, wherein said

moiety is selected from the group consisting of 1α previtamin D, 1α, 24-$(OH)_2$D2-aminoalkyl, 11α, 25-$(OH)_2$D2-aminoalkyl linked to the hydroxyl group at C-1, C-3, C-24 and C-25 of said vitamin D moiety and wherein the targeting moiety is bisphosphonate, **does not** reasonably provide enablement for (1) *any* conjugate comprising at last *any* one vitamin D moiety associated with a target molecule having an affinity for *any* tissue of interest, the targeting molecule moiety including at least one of *any* polyaspartic acid, *any* polyglutamic acid, *any* aminophosphosugar, *any* protein with bone mineral binding domains, *any* steroid, *any* metal ion-amino acid chelate, *any* antibody and combination thereof for targeting to tissue of interest such as bone or prostate. There is insufficient written description about the **structure** associated with function of *any* "vitamin D moiety" and *any* "targeting molecule moiety" such as *any* steroid other than DHEA and estrogen, *any* aminophosphosugar, *any* metal ion-amino acid chelate, *any* antibody and combination thereof for targeting to the tissue of interest such as bone and prostate for preventing abnormal cell growth such as hyperproliferation of any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest wherein the vitamin D moiety has a formula II as shown on page 11 lines 13-19 bridging page 12 lines 1 to 6 of the specification, wherein said moiety is selected from the group consisting of 1α previtamin D, 1α, 24-$(OH)_2$D2-aminoalkyl, 11α, 25-$(OH)_2$D2-aminoalkyl linked to the hydroxyl group at C-1, C-3, C-24 and C-25 of said vitamin D moiety and wherein the targeting moiety is bisphosphonate for targeting to tissue such as bone for treating bone loss.

The specification does not teach how to make and use *any* conjugate mentioned above because there is no structure associated with function of *any* "vitamin D moiety", and *any*

"targeting moiety", much less about the functions. Further, the targeting moiety including the ones such as the ones recited claim 44 have no define tissue specificity that would target the conjugate to specific tissue of interest such as bone and prostate, in turn, the conjugate would be useful for preventing abnormal cell growth such as hyperproliferation of any cell. The claims encompassed indefinite number of undisclosed conjugate having no specific structure.

Other than the six specific conjugate such as the ones recited in claim 45 for treating bone loss, there is insufficient guidance as to the target specificity of any antibody, much less targeting to the tissue of interest such as bone or prostate tissue for preventing abnormal growth and hyperproliferation of any cells. Likewise, there is insufficient guidance as to the structure of any polyaspartic acid, *any* polyglutamic acid, *any* aminophosphosugar, *any* protein with bone mineral binding domains, *any* steroid, *any* metal ion-amino acid chelate, much less about the target specificity of any conjugate.

It is well known that steroid such as testosterone binds to the androgen receptor and preferentially targets the conjugate to muscle rather than bone. Further, there is no in vivo working example demonstrating that *any* conjugate comprising *any* "vitamin D moiety" associated with *any* target molecule moiety such as testosterone would target the conjugate to tissue of interest such as bone for preventing bone loss, much less preventing abnormal growth such as hyperproliferation of any cells.

Bauss *et al* (of record) teach various conjugates such as 17β-estradiol-bisphosphonate conjugates BM 41.0825, BM 41.0871 and BM41.0825 and yet not all conjugates targeting to tissue of interest such as bone using bisphosphonates are effective for preventing bone loss (See abstract, in particular). Bauss *et al* further teach both estradiol and bisphosphonate alone have been shown to inhibit osteoporosis.

Christiansen *et al* (of record) teach various vitamin D in itself such as 1,25-dihydroxycholecalciferol (1,25(OH2)D3) or combined with estrogen for preventing postmenopausal osteoporosis (See Materials and methods, in particular). Christiansen *et al* further teach long-term treatment using vitamin D may cause side effects such as severe hypercalcemia and rental impairment (See page 308, column 1, in particular).

A pharmaceutical composition in the absence of in vivo data are unpredictable for the following reasons: (1) the conjugate may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the conjugate; (2) other functional properties, known or unknown, may make the conjugate

unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

16. Claims 41, 43, and 48 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "tissue is not plasma" in Claims 41, 43 and 48 represents a departure from the specification and the claims as originally filed because the negative limitation "not plasma" has no support in the specification. Further, applicants have not pointed out the support for said phrase in the amendment filed 8/14/02.

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

18. Claims 42 and 44-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "includes" in claim 42 and 45 is ambiguous because it is not clear whether the conjugate include the compounds such as the ones recited in claim 42 and 45 as a composition or the compounds are the conjugates. It is suggested that Applicant amend the claim using the Markush language such as the conjugate of claim 1 wherein the conjugate is selected

from the group consisting of 1α-(OH)-24-aminoalkyl-1, 1-bisphosphate D2 ....and combination thereof.

Likewise, the term "including" and "combination thereof" in claim 44 is ambiguous because it is not clear whether the target molecule moiety such as the ones recited in claim 44 is part of the conjugate or include along as a composition. If it is a conjugate, it is suggested that Applicant amend the claim using the Markush language. If it is not a conjugate, it is suggested that the preamble be changed to a composition comprising a conjugate.

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 1, 20, 41, 43, 44, 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi *et al* (of record, Analytical Biochemistry 244: 374-383, Jan 1997; PTO 892) or US Pat No. 4,292,250 (Sept 1981, PTO 892) each in view of Orme *et al* (Bioorg Med Chem Lett 4: 1375-1380, 1994; PTO 892) and US Pat No. 4,661,294 (April 1987, PTO 892).

The teachings of Kobayashi *et al* and the '250 patent have been discussed supra.

The claimed invention as recited in claim 44 differ from the references only that the target moiety having an affinity for tissue of interest is tetracycline.

The claimed invention as recited in claims 41, 43 and 48 differ from the references only that the conjugate with the proviso that the tissue is not plasma.

Orme *et al* teach a conjugate such as β-estradiol-3-benzoate-17-succinyl-12A-Tetracycline that targets to the tissue of interest such as bone (See page 1375, in particular). The reference steroid moiety such as β-estradiol-3-benzoate is associated with a target moiety such as Tetracycline having an affinity for a tissue of interest such as bone, which is not plasma (See Title, abstract, page 1375, in particular). The reference steroid moiety is associated with the target molecule moiety via a connecting group such as succinate ester which is a bifunctional connector that forms a bond between said steroid moiety and said target molecule moiety (See page 1376, in particular). Orme *et al* teach selective delivery of estrogen to bone tissue could result in a decrease in the side effects of estrogen therapy for the treatment of osteoporosis both by limiting systemic estrogen levels and by reducing the dosage required to achieve effective therapeutic results (See page 1375, second paragraph, in particular).

The '294 patent teaches various vitamin D moieties such as glycosylated, hydroxylated, fluorinated and glycosylated vitamin D are useful for treating vitamin D disorder such as hypoparathyroidism and bone disorder such as rickets, hyperproliferative skin disorder such as psoriasis and tumor, which possesses receptors for 1,25-dihydroxyvitamin D3.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the target molecule such as BSA or glucoronide in the vitamin D conjugate as taught by the Kobayashi *et al* and the '250 patent for the target molecule such as tetracycline as taught by Orme *et al* for a conjugate comprising at least one vitamin D moiety associated with a target molecule having an affinity for a tissue of interest such as bone. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Orme *et al* teach Tetracycline having an affinity for bone and selective delivery of estrogen to bone tissue could result in a decrease in the side effects of estrogen therapy for the treatment of osteoporosis both by limiting systemic estrogen levels and by reducing the dosage required to achieve effective therapeutic results (See page 1375, second paragraph, in particular).

The '294 patent teaches various vitamin D moieties such as glycosylated, hydroxylated, fluorinated and glycosylated vitamin D are useful for treating bone disorder such as rickets, or hyperproliferative skin disorder such as psoriasis and tumor, which possesses receptors for 1,25-dihydroxyvitamin D3.

In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

22. Claims 7 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi *et al* (of record, Analytical Biochemistry 244: 374-383, Jan 1997; PTO 892) or US Pat No. 4,292,250 (Sept 1981, PTO 892) each in view of Orme *et al* (Bioorg Med Chem Lett 4: 1375-1380, 1994; PTO 892), US Pat No. 4,661,294 (April 1987, PTO 892) as applied to claims 1 and 44 and further in view of Bauss *et al* (of record, Calcif Tissue Int 59: 168-173, 1996).

The teachings of Kobayashi *et al,* the '250 patent, Orme et al, and the '294 patent have been discussed supra.

The claimed invention as recited in claims 7 and 46 differ from the references only that the target moiety having an affinity for tissue of interest is bisphosphonate moiety.

Bauss *et al* teach bisphosphonates have been shown to have a high affinity for hydroxyapatide of bone and is useful as a bone resorption inhibitor in various metabolic bone disorders (See page 168, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the target molecule such as BSA or glucoronide in the vitamin D conjugate as taught by the Kobayashi *et al* and the '250 patent or the tetracycline as taught by Orme *et al* for the target molecule such as bisphosphonate as taught by Bauss *et al* for a conjugate comprising at least one vitamin D moiety associated with a target molecule having an affinity for a tissue of interest such as bone. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because bisphosphonates have been shown to have a high affinity for hydroxyapatide of bone and is useful as bone resorption inhibitors in various metabolic bone disorders as taught by Bauss *et al.* (See page 168, column 2, in particular). Orme *et al* teach Tetracycline having an affinity for bone and selective delivery of estrogen to bone tissue could result in a decrease in the side effects of estrogen therapy for the treatment of osteoporosis both by limiting systemic estrogen levels and

by reducing the dosage required to achieve effective therapeutic results (See page 1375, second paragraph, in particular). The '294 patent teaches various vitamin D moieties such as glycosylated, hydroxylated, fluorinated and glycosylated vitamin D are useful for treating vitamin D disorder such as hypoparathyroidism and bone disorder such as rickets, hyperproliferative skin disorder such as psoriasis and tumor, which possesses receptors for 1,25-dihydroxyvitamin D3.

In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

23. Claims 42 and 45 are free of prior art.

24. No claim is allowed.

25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any

inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

27. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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Technology Center 1600
November 4, 2002

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